GeneDx
207 Perry Parkway
Gaithersburg, MD 20877
Phone: 301-519-2100
Fax: 301-519-2892
E-mail: genedx@genedx.com
www.genedx.com

Test Information Sheet

SERPING1 (C1INH) Gene Analysis in Hereditary Angioedema (HAE)

Also known as: Hereditary angioedema Type I or II; Hereditary angioneurotic edema (HANE); C1 esterase inhibitor deficiency; C1 inhibitor; C1-INH

Mendelian Inheritance in Man Number:
106100 Hereditary Angioedema Type I and II;
606860 SERPING1 gene, aka C1NH gene, aka C1INH gene

***Clinical features*:**
Angioedema; episodic non-puritic, non-urticarial, non-pitting edema; laryngeal edema; GI symptoms including pain with visceral edema, nausea, diarrhea and vomiting. Trauma can precipitate or aggravate edema. In Type 1 HAE, C1 esterase inhibitor is quantitatively decreased while in Type II HAE, serum levels of the protein are normal or elevated, but activity is reduced. A third type, HAE III, is associated with mutations in a different gene (F12) that is not included in this test.

***Inheritance pattern*:** Autosomal dominant; de novo mutations occur in a minority of cases

***Reasons for referral*:**
1. Confirmation of a clinical diagnosis
2. Selection of appropriate prophylaxis and treatment
3. Genetic counseling
4. Identification of at-risk family members
5. Prenatal diagnosis

***Test method*:**
Analysis is performed by bi-directional sequencing of each of the seven coding exons (exons 2-8) of the SERPING1 gene plus targeted array CGH analysis with exon-level resolution (ExonArrayDx) to evaluate for deletions and duplications of one or more exons. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

***Test sensitivity*:**
Germline mutations in SERPING1 have been found in nearly all patients with the clinical findings of hereditary angioedema and deficient levels or activity of C1 esterase inhibitor. About 82% of patients have mutations that are identifiable by sequencing while ~17% have gross duplications or deletions. Both strategies are employed in this test. Only about 1% of mutations are located in the promoter or are otherwise not detectable with this test.[1,2,3]

Mutation spectrum:
Mutations are dispersed throughout the SERPING1 gene, and include missense, frameshift, nonsense, splice-site, promoter, and in-frame small deletion/insertion mutations. In addition, this gene is predisposed to gross rearrangements due to numerous intragenic *Alu* repeats.[4]

Specimen Requirements and Shipping/Handling:

- *Blood*: A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- *Buccal Brushes*: **CANNOT be accepted for this test.**
- *Prenatal Diagnosis:* 10 mL amniotic fluid, 5 mg CVS, or 2 T25 flasks. Ship overnight at ambient temperature, using a cool pack in hot weather. Call to discuss requirements for parental blood. Keep backup cultures.

Required Forms:

- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

Prices and Turn-Around Time - *Fees are subject to change without notice:*

Test #2341: Gene sequencing and ExonArrayDx testing in a new patient = $ 1600; Approx. 6-8 weeks
Test #9011: Testing of a relative for one specific known mutation* = $ 350; Approx. 2-3 weeks
Test #902: Prenatal diagnosis for a specific known mutation* = $ 2000; Approx. 2 weeks

***** Please see our website for CPT codes/prices for carrier and prenatal testing: http://www.genedx.com

CPT codes for mutation detection in a new patient - *All codes and units apply:*

83891 x 16 units = $ 100
83898 x 16 units = $ 400
83894 x 16 units = $ 80
83904 x 16 units = $ 432
88386 x 1 unit = $ 488
83892 x 2 units = $ 40
83912 x 2 units = $ 60

TOTAL $ 1600

Possible ICD9 Codes:

Hereditary Angioedema: 277.6

References:

1. Kalmár, L. et al., HAEdb: A Novel Interactive, Locus-Specific Mutation Database for the C1 Inhibitor Gene. *Hum Mutat.* 25: 1-5, 2005.
2. Kalmár, L. et al., Mutation Screening for the C1 Inhibitor Gene Among Hungarian Patients With Hereditary Angioedema. *Hum Mutat*. 22:498, 2003.
3. Bowen, B. et al., A Review of the Reported Defects in the Human C1 Esterase Inhibitor Gene Producing Hereditary Angioedema Including Four New Mutations. *Clin Immunol.* 98: 157-163, 2001.
4. Stoppa-Lyonnet et al. Recombinational Biases in the Rearranged C1-Inhibitor Genes of Hereditary Angioedema Patients, Am J Hum Genet 49:1055, 1991.

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WHERE Rare is Common

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F12 Gene Testing in Hereditary Angioedema (HAE) Type III

Mendelian Inheritance in Man Number:

610618 Hereditary angioedema type III; hereditary angioedema with normal C1 inhibitor activity
610619 F12 Gene (Coagulation factor XII, Hageman factor)

***Clinical features*:**

Hereditary angioedema type III is characterized primarily by skin swellings (predominantly facial) and abdominal attacks. Additional symptoms that may occur are tongue swellings, laryngeal edemas and swellings of the soft palate. Affected individuals are predominantly women, though men can be affected, typically at a later age of onset and with less frequency and severity of attacks. Factors that can influence the onset and frequency of angioedemic attacks include trauma and increased estrogen levels. Nearly 60% of women experienced onset of symptoms after initiation of oral contraceptives or during the first pregnancy[1]. Features that distinguish HAE type III from types I and II include: presence of normal C1 inhibitor activity levels, average later age of onset (typically in the 2nd decade of life), predominance of facial swelling as compared to swellings of the extremities and sex bias.

***Inheritance pattern*:**

Autosomal dominant with variable expressivity, incomplete penetrance and sex bias.

Reasons for referral:

1. Confirmation of a clinical diagnosis
2. Selection of appropriate prophylaxis and treatment
3. Genetic counseling
4. Identification of at-risk family members
5. Prenatal diagnosis in at-risk pregnancies

***Test method*:**

Using genomic DNA obtained from the submitted biological material, bi-directional sequence of exon 9 of the F12 gene is obtained using 2 independent sets of primers and analyzed for any mutation of codon 328, corresponding to amino acid Thr309 in the mature processed protein. If a sequence change is identified, the mutation is confirmed by a second sequence analysis.

***Test sensitivity*:**

In an early study, approximately 25% of individuals with a clinical diagnosis of HAE type III had a mutation in the F12 gene at codon Thr328. Nearly 85% of those individuals had the Thr328Lys (T328K) mutation, while the remainder had the Thr328Arg (T328R) mutation[1]. The method used by GeneDx to screen the F12 gene is expected to identify any mutations that occur at this site in the gene with a sensitivity greater than 99%.

Mutation spectrum:

Only two mutations have been reported in the F12 gene in association with HAE type III. Both affect codon 328 in exon 9: Thr328Lys and Thr328Arg. In the mature processed protein, this position

becomes Thr309, so these mutations have also been called Thr309Lys (T309K) and Thr309Arg (T309R).

Specimen Requirements and Shipping/Handling:

- *Blood*: A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for up to 7 days prior to shipping.
- *Prenatal Diagnosis:* 10 mL amniotic fluid, 5 mg CVS, or 2 T25 flasks. Ship overnight at ambient temperature, using a cool pack in hot weather. Call to discuss requirements for parental blood. Keep backup cultures.

Required Forms:

- Sample Submission (Requisition) Form – complete all pages, including
- Payment Options Form or Institutional Billing Instructions

Prices and Turn-Around Time - *Fees are subject to change without notice:*

Test #388: Sequencing of exon 9 the F12 gene in a new patient = $350; 3 weeks
Test #9021: Prenatal diagnosis for a specific known mutation(s)* = $2000; Approx. 2 weeks

***** Please see our website for CPT codes/prices for prenatal testing: http://www.genedx.com.

CPT codes for mutation detection in a new patient - *All codes and units apply:*

83891 x	2 units =	$ 20
83898 x	2 units =	$ 70
83894 x	2 units =	$ 40
83904 x	4 units =	$ 120
83892 x	2 units =	$ 40
83912 x	2 units =	$ 60
TOTAL		**$ 350**

Possible ICD9 Codes: Hereditary Angioedema: 995.1

References Cited*:*

1. Bork K. et al., Hereditary angioedema caused by missense mutations in the factor XII g ene: Clinical features, trigger factors, and therapy. *J Allergy Clin Immunol*. 2009 Jul;124(1):129-34.
2. Cichon S. et al., Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet*. 2006 Dec;79(6):1098-104.
3. Dewald G. and Bork K., Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2006 May 19;343(4):1286-9.
4. Martin L. et al., Hereditary angioedema with normal C1 inhibitor gene in a family with affected women and men is associated with the p.Thr328Lys mutation in the F12 gene. *J Allergy Clin Immunol*. 2007 Oct;120(4):975-7.

